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Is Increased Hepatitis C Virus Case-Finding Combined With Current or 8-Week to 12-Week Direct-Acting Antiviral Therapy Cost-Effective in UK Prisons? A Prevention Benefit Analysis

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Prisoners have a high prevalence of hepatitis C virus (HCV), but case-finding may not have been cost-effective because treatment often exceeded average prison stay combined with a lack of continuity of care. We assessed the cost-effectiveness of increased HCV case-finding and treatment in UK prisons using short-course therapies. A dynamic HCV transmission model assesses the cost-effectiveness of doubling HCV case-finding (achieved through introducing opt-out HCV testing in UK pilot prisons) and increasing treatment in UK prisons compared to status quo voluntary risk-based testing (6% prison entrants/year), using currently recommended therapies (8-24 weeks) or interferon (IFN)-free direct-acting antivirals (DAAs; 8-12 weeks, 95% sustained virological response, £3300/week). Costs (British pounds, £) and health utilities (quality-adjusted life years) were used to calculate mean incremental cost-effectiveness ratios (ICERs). We assumed 56% referral and 2.5%/25% of referred people who inject drugs (PWID)/ex-PWID treated within 2 months of diagnosis in prison. PWID and ex-PWID or non-PWID are in prison an average 4 and 8 months, respectively. Doubling prison testing rates with existing treatments produces a mean ICER of £19,850/quality-adjusted life years gained compared to current testing/treatment and is 45% likely to be cost-effective under a £20,000 willingness-to-pay threshold. Switching to 8-week to 12-week IFN-free DAAs in prisons could increase cost-effectiveness (ICER £15,090/quality-adjusted life years gained). Excluding prevention benefit decreases cost-effectiveness. If >10% referred PWID are treated in prison (2.5% base case), either treatment could be highly cost-effective (ICER<£13,000). HCV case-finding and IFN-free DAAs could be highly cost-effective if DAA cost is 10% lower or with 8 weeks' duration. *Conclusions:* Increased HCV testing in UK prisons (such as through opt-out testing) is borderline cost-effective compared to status quo voluntary risk-based testing under a £20,000 willingness to pay with current treatments but likely to be cost-effective if short-course IFN-free DAAs are used and could be highly cost-effective if PWID treatment rates were increased. (HEPATOLOGY 2016;63:1796-1808)

Hepatitis C virus (HCV) is a blood-borne virus which can result in cirrhosis, liver failure, hepatocellular carcinoma, and death. In most developed country settings the majority of transmission occurs among people who inject drugs (PWID). In the United Kingdom, >90% of ongoing transmission occurs

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; HCV, hepatitis c virus; ICER, incremental cost-effectiveness ratio; IFN-free, interferon-free; pegIFN, pegylated interferon; PWID, people who inject drugs; QALY, quality adjusted life-year; RBV, ribavirin; SVR, sustained virological response; WTP, willingness to pay.

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among PWID, and >80% of chronic HCV infection is among current or ex-PWID.[1] Previous treatments with pegylated interferon and ribavirin (pegIFN+RBV) were long (24-48 weeks), were poorly tolerated, and cured roughly half of individuals. The advent of new short-course, better-tolerated, and highly effective HCV treatments which can cure >80% of individuals makes identifying those who are chronically infected an urgent priority.[2] HCV case-finding in specialist drug clinics and primary care is recommended and cost-effective, especially with increased treatment rates.[3,4]

Although there are high numbers and proportions of PWID in prison, testing rates are relatively low (6% prison entrants were tested for HCV in England in 2013[5]). Previous analyses suggested that the cost-effectiveness of increasing HCV case-finding in UK prisons was conditional on a high level of continuity of care between prison and community and unlikely to be cost-effective in the absence of any continuity.[3] This was because of the conflict between short incarceration times for PWID (estimated average 4 months in England) and long treatment durations (24-48 weeks) required with pegIFN+RBV treatment.

The current standard of care in UK prisons is voluntary HCV testing offered to prisoners who consider themselves at risk, leading to approximately 6% of prison entrants tested per year. In 2014, opt-out testing for blood-borne viruses (HCV, hepatitis B virus, and human immunodeficiency virus) was introduced in selected prisons in England,[6] which doubled the numbers of HCV tests in these pilot prisons. Hence, this opt-out program is likely to increase the numbers tested and initiated onto HCV treatment from within the prison setting. However, suboptimal treatment delivery (roughly half of HCV-infected cases are referred to specialist care, with one-quarter of those referred initiating treatment,[7] of which many will have interrupted treatment due to prison release) may limit the benefit of testing interventions. Shorter-duration (8-12 weeks) interferon (IFN)-free direct-acting antiviral (DAA) therapy with high sustained virological response (SVR) rates (>90%)[2] could allow more to successfully complete treatment within their prison stay.

We assessed the cost-effectiveness of increased HCV testing and treatment rates in English prisons (such as through opt-out programs, which doubled testing in UK pilot prisons) compared to status quo testing rates combined with currently available HCV treatments or future 8-week to 12-week IFN-free DAA therapy, including individual and prevention benefits.

Materials and Methods

MATHEMATICAL MODEL

We adapted a dynamic model of incarceration and HCV transmission among PWID in England.[3,4] Full

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details of the model structure and calibration can be found in previous publications[3,4] and the Supporting Information. Overall, the model tracks incarceration, initiation and cessation of injecting, HCV transmission among PWID only (in both prison and the community; imprisoned PWID can only transmit to other prisoners) and HCV testing and treatment through various settings present in the United Kingdom (prison, addiction services, general population, and other). The model is dynamic in that a PWID's risk of acquiring HCV is proportional to the setting-specific HCV prevalence (prison, community), which can change over time. The model simulates the background rate of testing and treatment occurring in the community and prison, such that individuals can be identified in either setting.

The model includes stratification by injecting state (never PWID/PWID/former PWID), incarceration status (never/currently/formerly), contact with addiction services (in contact/not in contact), age (15-19, 20-24, 30-54, 55-64, 65-74, 75+), and HCV infection and disease progression (never infected, spontaneously cleared, mild HCV, moderate HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, posttransplant). HCV disease stages are further subdivided into undiagnosed or diagnosed, where those who are diagnosed can either be lost to follow-up, in referral, on antiviral treatment, achieved SVR, or non-SVR. Because no data are available on continuity of care between the prison and community, we assumed that those who are in referral or on treatment are lost-to follow-up when entering or leaving prison, in line with our previous analyses.[3,4]

We include updated treatment SVR and durations with new and upcoming IFN-free DAA therapies as well as progression for those in the cirrhosis SVR stage (at reduced rates compared to non-SVR), in accordance with recent data.

MODEL CALIBRATION

We performed a probabilistic uncertainty analysis where 1000 parameter sets were sampled from each parameter uncertainty distribution in Table 1. For each parameter set, the model was calibrated to UK epidemiological data on incarceration, injecting drug use, HCV prevalence, and diagnosis. Further calibration details can be found in our previous publications[3,4] and the Supporting Information. After calibration, for each of the 1000 parameter sets, the model was used to simulate the baseline and intervention scenarios.

BASELINE

The baseline scenario assumes status quo rates of HCV voluntary risk-based testing (mean 6% of prison entrants tested annually) and treatment with current (provisionally approved by the National Institute for Health and Care Excellence) therapies.[8,9] The current therapies modeled are as follows: genotype 1: sofosbuvir/ledipasvir for genotype 1 patients without cirrhosis (8 weeks) and with cirrhosis (12 weeks); genotype 2: pegIFN+RBV for 24 weeks; genotype 3: pegIFN+RBV for 24 weeks for patients without cirrhosis and sofosbuvir+ pegIFN+RBV for 12 weeks for patients with cirrhosis; genotype 4: sofosbuvir/ledipasvir for 12 weeks. Based on an estimated genotype distribution of 50% genotype 1/4, 5% genotype 2, and 45% genotype 3, the mean average SVR for this scenario is 87%.

INTERVENTION

We examined a doubling of HCV testing in prison (to a mean 12% of prison entrants per year) due to a scale-up of opt-out testing (as achieved during phase 1[6]) with various treatment scenarios:

1. *Status quo treatments:* Doubling of HCV testing in prison with current treatments (as in the baseline, mean average SVR 87%) in prison and the community
2. *8-week to 12-week IFN-free DAAs:* Doubling of HCV testing in prison with 8-week to 12-week IFN-free DAAs with 95% SVR in prison (8 weeks G1 patients without cirrhosis, 12 weeks all others) and current treatments (as in the baseline) in the community
3. *Treatments as in (1) and (2) but with treatment scale-up for PWID:* The scenarios above (status quo, 8-week to 12-week IFN-free DAAs) but with varied levels of HCV treatment for PWID in prison (up to 25% after referral compared with a mean of 2.5% at base case)

COST-EFFECTIVENESS METHODS

We performed our analysis from the UK National Health Service perspective as HCV testing and treatment are paid for by the National Health Service. Costs (in 2014 British pounds, £1 = $1.50) and health utilities (in quality adjusted life-years [QALYs]) were attached to each model state and discounted at 3.5% per year per the National Institute for Health and Care

TABLE 1. Model Parameters

	Mean value	Distribution	Reference
Transition probabilities per year (all probabilities converted to instantaneous rates)			
Mild to moderate	0.025	Beta (α = 38.0859, β = 1485.3516)	(19)
Moderate to CC	0.037	Beta (α = 26.905, β = 700.2582)	(19)
CC to DC	0.039	Beta (α = 14.6168, β = 360.1732)	(19)
CC/DC to HCC	0.014	Beta (α = 1.9326, β = 136.1074)	(19)
CC SVR to DC (relative risk of non-SVR)	0.07	Log normal (95% CI 0.03-0.20)	(20,21)
CC/DC SVR to HCC (relative risk of non-SVR)	0.23	Log normal (95% CI 0.16-0.35)	(22)
DC/HCC to LT	0.03	Beta (α = 6.5256, β = 210.9945)	(19)
DC to death	0.13	Beta (α = 147.03, β = 983.97)	(19)
HCC to death	0.43	Beta (α = 117.1033, β = 155.23)	(19)
LT to death	0.21	Beta (α = 16.2762, β = 61.2294)	(19)
Posttransplant to death	0.057	Beta (α = 22.9017, β = 378.8825)	(19)
Health state utilities/disutilities per year			
Ex-PWID age 15-19			
Uninfected	0.94		(38)
Mild	0.77	Beta (α = 521.2375, β = 155.6943)	(19,39)
Moderate	0.66	Beta (α = 168.2461, β = 86.6723)	(19,39)
Cirrhosis	0.55	Beta (α = 47.1021, β = 38.5381)	(19,39)
DC	0.45	Beta (α = 123.75, β = 151.25)	(19,39)
HCC	0.45	Beta (α = 123.75, β = 151.25)	(19,39)
LT	0.45	Beta (α = 123.75, β = 151.25)	(19,39)
Posttransplant	0.67	Beta (α = 59.2548, β = 29.1852)	(39,40)
Treatment IFN-containing, decrement	0.11		(19,39)
Treatment IFN-free, decrement	0.06		(8)
Mild SVR	0.82	Beta (α = 65.8678, β = 14.4588)	(19,39)
Moderate SVR	0.72	Beta (α = 58.0608, β = 22.5792)	(19,34,39)
Cirrhosis SVR	0.61	Beta (α = 58.0476, β = 37.1124)	(40)
PWID age 15-19			
Uninfected	0.74	Uniform (0.67-0.8)	(41)
HCV disease states	As in ex-PWID but reduced by PropPWID*		Assumed
Disutility with age			
20-24	0		(38)
25-29	0.005		(38)
30-54	0.049		(38)
55-64	0.14		(38)
65-74	0.16		(38)
75+	0.21		(38)
Costs (£ per year, except where noted)			
Mild diagnosed	178	PPI† × Gamma (κ = 25.6995, θ = 5.3698)	(19,39)
Moderate diagnosed	925	PPI × Gamma (κ = 88.8502, θ = 8.0698)	(19,39)
Cirrhosis diagnosed	1468	PPI × Gamma (κ = 24.2342, θ = 46.9584)	(19,39)
DC	11,765	PPI × Gamma (κ = 36.0249, θ = 253.1582)	(19,39)
HCC	10,484	PPI × Gamma (κ = 18.1081, θ = 448.8045)	(19)
LT (per transplant)	35,256	PPI × Gamma (κ = 89.7536, θ = 304.5004)	(19)
Cost of care in year of LT	12,201	PPI × Gamma (κ = 13.7788, θ = 686.4168)	(19)
Posttransplant	1787	PPI × Gamma (κ = 15.2189, θ = 91.0053)	(19)
Mild SVR	334	PPI × Gamma (κ = 28.8141, θ = 8.9887)	(19)
Moderate SVR	925	PPI × Gamma (κ = 88.8502, θ = 8.0698)	(19)
Cirrhosis SVR	1468	PPI × Gamma (κ = 24.2342, θ = 46.9584)	(19)
Undiagnosed states	0		
Drug costs, per week§			
pegIFN+RBV	228		(24)
SOF+PR	3143		(24)
SOF/ledipasvir	3248		NHS list price
"Future" IFN-free DAAs	3300		
Treatment delivery, per week§			
Ex-PWID	90		(19)
PWID (proportion ex-PWID cost)	120%		(3,23)
Testing costs in community#	121	Uniform ± 50%	(3,42)
Testing costs in prison#	151	Uniform ± 60%	(3,42)
PCR RNA test (if antibody-positive)	78	Uniform ± 20%	(3,42)

TABLE 1. *Continued*

	Mean value	Distribution	Reference
Testing and treatment parameters			
Proportion PWID diagnosed (initial)	50%		(5)
Proportion PWID treated (initial)	0%		Assumption
Proportion ex-PWID diagnosed (initial)	30%	Uniform (24%-36%)	Assumption (14)
Proportion of diagnosed ex-PWID treated (initial)	10%	Uniform (5%-15%)	(43)
HCV genotype (proportion)[§]			
G1	45%		(5)
G2	5%		
G3	45%		
G4	5%		
SVR[§]			
IFN/RBV G2/G3 mild/mod	0.8	Uniform (0.75-0.85)	(44,45)
IFN/RBV G2 cirrhosis	0.6	75% reduction from mild to moderate	(46)
Harvoni G1/G4 noncirrhosis	0.93	Uniform (0.9-0.96)	(47)
Harvoni G1/G4 cirrhosis	0.94	Triangular (min 0.9, max 0.99)	(48)
SOF+PR G3 cirrhosis	0.83	Triangular (min 0.52, max 0.98)	(49)
Future IFN-free DAAs	0.95		Assumption
Antiviral treatment duration (weeks)[§]			
Harvoni G1 noncirrhosis	8		(9)
Harvoni G1 cirrhosis, G4	12		(9)
pegIFN/RBV G2	24		(44)
pegIFN/RBV G3 noncirrhosis	24		(44)
SOF+PR G3 cirrhosis	12		(8)
Proportion referred			
Prison	56%	Uniform (41%-70%)	(15)
Community	86%	Uniform (80%-90%)	
Proportion referred who initiate treatment within 1 year (excl. prison)			
Ex-PWID	50%	Uniform (40%-60%)	(35,50)
PWID	5%	Uniform (1%-10%)	Assumption (51)
Treatment initiation rate after first year in referral (excl. prison) per year			
Ex-PWID	10%	Uniform (5%-15%)	Assumption
PWID	3%	Uniform (1%-5%)	Assumption (51)
Proportion referred who initiate treatment in prison within 2 months			
Ex-PWID	25%	Uniform (20%-30%)	(6,7)
PWID	2.5%	Uniform (0%-5%)	Assumption (51)
Yield (proportion tests antibody-positive)			
General	2.7%		[‡]
Prison	14.7%		[‡]
Addiction services	17.7%		[‡]
Other	1.7%		[‡]
Distribution of PWID HCV tests			
General	38.4%		[‡]
Prison	11.5%		[‡]
Addiction services	29.4%		[‡]
Other	20.7%		[‡]

*PropPWID = uninfected PWID utility value for age 15-19/uninfected ex-PWID utility for age 15-19.
[†]PPI = Hospital and Community Health Services Pay and Prices Index inflation factor from 03/04 to 13/14 (1.29).
[‡]Health Protection Agency unpublished data from the 2010 Sentinel Surveillance.
[§]Used to calculate an average weighted treatment cost, SVR, and treatment duration.
[#]Includes assessment, pretest discussion, test, posttest results, and enzyme-linked immunosorbent assay. Includes additional assessment time in prison (20 minutes with nurse).
Abbreviations: CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; NHS, National Health Service; PCR, polymerase chain reaction; PR, pegylated interferon and ribavirin; SOF, sofosbuvir.

Excellence guidelines. We used a 100-year time horizon to accrue both individual and population benefits. We calculated the mean incremental cost-effectiveness ratio (ICER) by dividing the difference in mean costs by the difference in mean QALYs between the intervention and its comparator. We performed an incremental analysis where the ICERs are calculated for each intervention after ranking the alternatives from least to most costly. We determined cost-effectiveness using UK willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained and denoted an intervention as highly cost-effective using a WTP

threshold of £13,000, in line with a recent estimate of where the UK WTP should lie.[10] Cost-effectiveness acceptability curves are presented. Multiple one-way sensitivity analyses were undertaken.

PARAMETERIZATION

HCV Prevalence and Cascade of Care

We modeled a scenario with a 35% baseline HCV chronic prevalence among PWID (approximately 45% antibody prevalence among PWID as found in the United Kingdom,[11] assuming 26% spontaneously clear the virus[12]). Based on differential incarceration rates by age, this results in a mean fitted HCV chronic prevalence among PWID of 35% in the community and 34% in prison and an HCV incidence of 8.8 per 100 person-years (95% confidence interval [CI] 5.9-13.4 per 100 person-years) in the community and 8.3 per 100 person-years (95% CI 5.8-12.7 per 100 person-years) in prison. We assumed HCV prevalence among PWID is at steady state based on the stable prevalence exhibited among PWID in contact with drugs services from 2003 through 2013.[13] We assumed that 50% of PWID[5] and 30% of ex-PWID[14] were diagnosed initially in 2014. Setting-specific testing rates in prison and the community for PWID and ex-PWID have been estimated[3,4]; see the Supporting Information for more details on community testing and cascade of care assumptions. Overall, we estimated ~6% of prison entrants tested per year, consistent with reported testing rates prior to the introduction of opt-out testing (6% in 2013[5]). Of those tested, ~15% are HCV antibody-positive. A recent UK study reported a 56% referral rate from testing services to specialist care in prison.[15] The time from testing to treatment initiation in prison is unknown; estimated time to referral in prison is 4 weeks,[6] so we assumed treatment initiation within 2 months of diagnosis in prison. Among a national survey across English prisons in 2012, 28% of patients referred to specialist care commenced treatment in the same year,[7] but it is unknown what proportion were PWID. Hence, we assumed 25% of ex-PWID commence treatment within 2 months of diagnosis in prison. Community PWID treatment rates in the United Kingdom are low (<25 per 1000 PWID annually), and due to the short sentences for PWID (4 months) and challenges with continuity of care after transfer or release, it is likely prison treatment rates are similarly low. Hence, we assumed that 2.5% (sampled from 0%-5%) of those PWID referred to specialist care from prison commence treatment within 2 months at baseline.

Incarceration Parameters

The model was parameterized and calibrated to detailed UK data on incarceration patterns among PWID and the general population. We calibrated the model to 10,000 prisoners incarcerated at a given time (approximately 5,000,000 total individuals based on a 0.2% incarceration prevalence among the general population[16,17]). See Martin et al.[3,4] and the Supporting Information for more details.

HCV DISEASE PROGRESSION AND HEALTH UTILITIES

Parameters for HCV disease progression and health utilities were taken from published UK economic evaluations[3,18,19] and recent data on progression from cirrhosis after SVR.[20,21] These assumptions result in a mean 12% progression to cirrhosis within 20 years of infection without treatment, consistent with published estimates.[22]

COSTS

Costs related to HCV disease stages, HCV testing, and HCV treatment were taken from previous UK economic evaluations[3,19,23] and the British National Formulary.[24] We assumed individuals with undiagnosed HCV would not incur health care costs until progressing to decompensated cirrhosis. Costs were inflated to 2014 British pounds using the Health and Community Hospital Service pay and prices index. Although we include costs for testing, we do not include additional costs for the testing scale-up as no additional funding was provided to the pilot prisons of the opt-out program.

SENSITIVITY ANALYSES

We performed matched univariate sensitivity analyses on the following parameters: discount rate (0% and 6% compared to 3.5% at base case), IFN-free SVR (90% compared to 95% at base case), IFN-free treatment duration (8 weeks compared to 8-12 weeks at base case), DAA drug cost (25% reduction compared to base case), proportion referred for treatment (100% versus 56% at base case), time horizon (50 compared to 100 years at base case), yield (30% reduction compared to 0% at base case), and no prevention benefit

TABLE 2. Cost-Effectiveness Results

	Mean incremental costs (£) per 10,000 prisoners* (95% CI)	Mean incremental QALYs per 10,000 prisoners* (95% CI)	Mean ICER (£ per QALY gained)
Double testing and provide status quo treatment	8,362,599† (5,021,130-13,747,661)	421.27† (172.93-789.53)	19,851†
Double testing and provide 12-week IFN-free DAA therapy in prison	2,584,159‡ (872,364-6,078,955)	171.25‡ (46.89-396.74)	15,090‡

*We calibrated the model to 10,000 prisoners incarcerated at a given time (approximately 5,000,000 total individuals based on a 0.2% incarceration prevalence among the general population[15,16]) and tracked individuals both in the community and those who cycle in/out of prison.
†Compared to the status quo testing and treatment scenario.
‡Compared to the double testing and status quo treatment scenario.

for 2.5% and 10% referred PWID treated scenarios (2.5% referred PWID treated and prevention benefit included in base case).

Results

DOUBLING OF HCV TESTING IN PRISON WITH STATUS QUO TREATMENTS

Doubling testing in prison and providing status quo HCV treatments results in approximately 2400 HCV tests annually per 10,000 prisoners (~19,500 entrants), of which a mean of 353 are HCV antibody-positive, 261 are HCV RNA+, 146 are referred to treatment, and 21 are initiated onto treatment. Despite assuming a mean SVR of 87%, due to treatment interruption and assuming no continuity of care on release, the mean effective SVR is 40% (95% CI 38-46). The intervention results in mean incremental costs of £8,362,599 (95% CI £5,021,130-13,747,661) per 10,000 prisoners and mean incremental QALYs gained of 421.27 (95% CI 172.93-789.53) compared to status quo testing and treatment (Table 2). This strategy results in a mean ICER of £19,851 per QALY gained and is 45% and 85% likely to be cost-effective at a £20,000 or £30,000 per QALY gained WTP threshold, respectively (Fig. 1A).

DOUBLING OF HCV TESTING IN PRISON WITH 8-WEEK TO 12-WEEK IFN-FREE DAAS WITH 95% SVR IN PRISON

If HCV testing in prison is doubled and a switch to 8-week to 12-week IFN-free DAA therapy is provided with 95% SVR in prison, costs increase due to provision of DAA therapy for all genotypes (mean incremental costs £2,584,159, 95% CI £872,364-6,078,955, per 10,000 prisoners compared to doubled testing with status quo treatments), but QALYs are gained (171.25, 95% CI 46.89-396.74) due to a combination of increased SVR and shorter treatment duration for genotype 2 and 3 patients without cirrhosis from 24 to 12 weeks (Table 2). Overall, this results in a mean ICER of £15,090 per QALY gained compared to doubled testing and status quo treatments and is 84% and 96% likely to be cost-effective at a £20,000 or £30,000 per QALY gained WTP threshold, respectively (Fig. 1B). Despite assuming a mean SVR of 95%, the mean effective SVR is 46% (95% CI 43-53%). In this scenario, roughly half the benefit is due to shortening treatment; with only a shortening of treatment (but SVR rates equal to the status quo scenario) the intervention gains 79.67 QALYs (95% CI 22.8-177.21).

DOUBLING HCV TESTING WITH INCREASED PWID HCV TREATMENT RATES IN PRISON

Increasing PWID treatment rates after referral in prison results in significant increases in the cost-effectiveness of doubled testing using current treatments (Fig. 2A) or if 8-week to 12-week IFN-free DAAs are introduced (Fig. 2B). If 10% of PWID are treated after referral in prison, the ICERs for both treatment interventions drop below £13,000/QALY gained (£12,691/QALY with current treatments and £6461/QALY gained with 8-week to 12-week IFN-free DAAs). In this scenario, doubling testing with current treatments is 47% and 93% likely to be cost-effective under £13,000 and £20,000 WTP thresholds, respectively, and is 99% likely to be cost-effective under a £13,000 WTP threshold with 8-

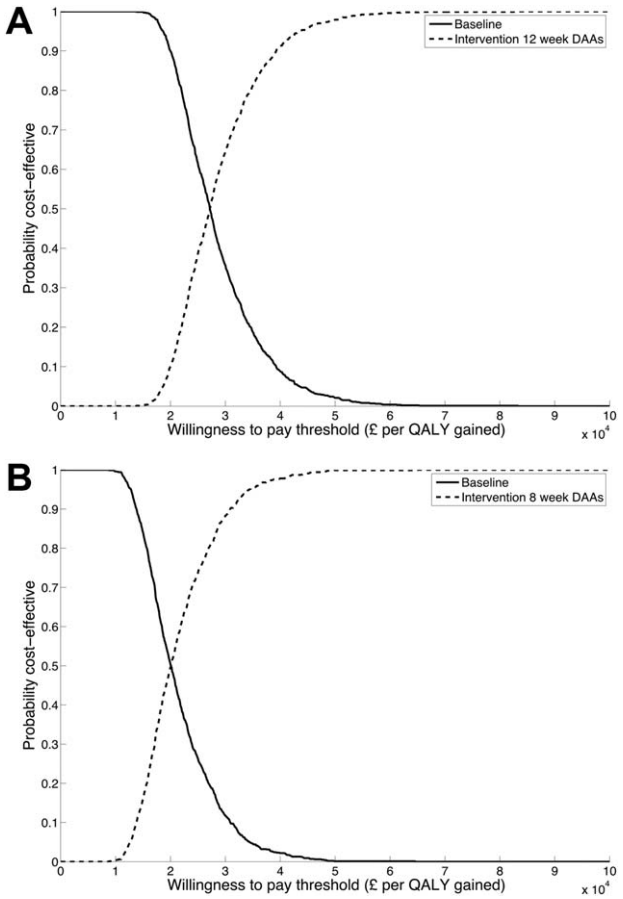

FIG. 1. Cost-effectiveness acceptability curves for doubled HCV case-finding in prison combined with (A) status quo treatments and (B) 8-week to 12-week IFN-free DAAs in prison. Incremental comparisons shown are (A) doubled HCV case-finding in prison combined with status quo treatments compared to status quo testing/treatment and (B) doubled HCV case-finding combined with 8-week to 12-week IFN-free DAAs in prison compared to doubled case-finding with status quo treatments.

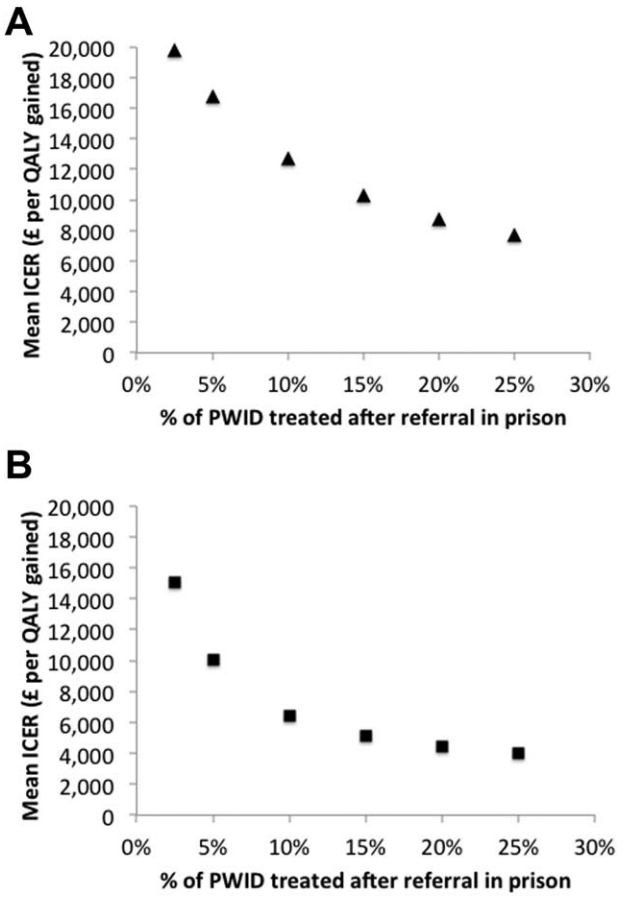

FIG. 2. Changes in mean ICER with increased PWID treatment rates in prison (2.5%-25% after referral). Base-case analysis assumes a mean of 2.5% PWID treated after referral in prison. (A) Doubled testing with status quo treatments compared to status quo testing/treatment. (B) Double testing with 8-week to 12-week IFN-free DAAs compared to doubled testing with status quo treatments.

week to 12-week IFN-free DAAs. If 25% of PWID are treated after referral, the ICER drops to below £8000 and £4000 per QALY gained for the status quo treatment scenarios and 8-week to 12-week IFN-free DAA scenarios, respectively.

SENSITIVITY ANALYSIS

When performing a univariate sensitivity analysis on the mean ICER with status quo treatments (Fig. 3A), we found that enhancements in the cascade of care increased cost-effectiveness and that population prevention benefits increase as treatment rates for PWID increase. If 100% of patients were referred in prison (56% at base case), the mean ICER dropped to just over £15,000/QALY. Turning off the prevention benefit at base case led to marginal reductions in cost-effectiveness because PWID treatment rates were very low at baseline, so little prevention benefit accrued (mean ICER £22,051/QALY gained versus £19,851/QALY gained with prevention benefits). However, the prevention benefit substantially increases with increased treatment rates; treating 10% of referred PWID in prison leads to a mean ICER of £20,064/QALY gained without prevention benefits but is highly cost-effective with prevention benefits included (mean ICER £12,495/QALY gained, Fig. 3A).

For all other analyses, the only analysis which increased the ICER above £30,000/QALY was if the doubled testing was associated with a 30% drop in yield (mean ICER £32,893; no change in base case). Shortening the time horizon (50 years compared to 100 years at base case) and increasing the discount rate (6% compared to 3.5% at base case) increased the mean ICER, but it remained below £30,000/QALY (Fig. 3A). Reducing the discount rate to 0% (3.5%/year at base case) and lowering the cost of DAAs in prison by 10% or 25% reduced the ICER (Fig. 3A).

Qualitative results were similar with the sensitivity analysis on the mean ICER using 8-week to 12-week IFN-free treatments; all scenarios led to ICERs below £30,000/QALY (Fig. 3B). We additionally found that if IFN-free SVR was 90% (instead of 95%), the ICER remained below £20,000/QALY (£19,325/QALY). When switching to IFN-free DAAs, the ICER is sensitive to DAA drug cost; if the price of IFN-free DAAs is reduced by 10%, the mean ICER drops to below £13,000/QALY gained. If 8-week IFN-free therapies for all genotypes are provided in prison, the mean ICER dropped to £6180/QALY. Although this scenario resulted in a slightly higher effective SVR due to greater treatment completion (mean effective SVR 48% overall versus 46% with 8-week to 12-week treatments), the main improvement in cost-effectiveness was the result of reduced cost of treatment due to shorter durations.

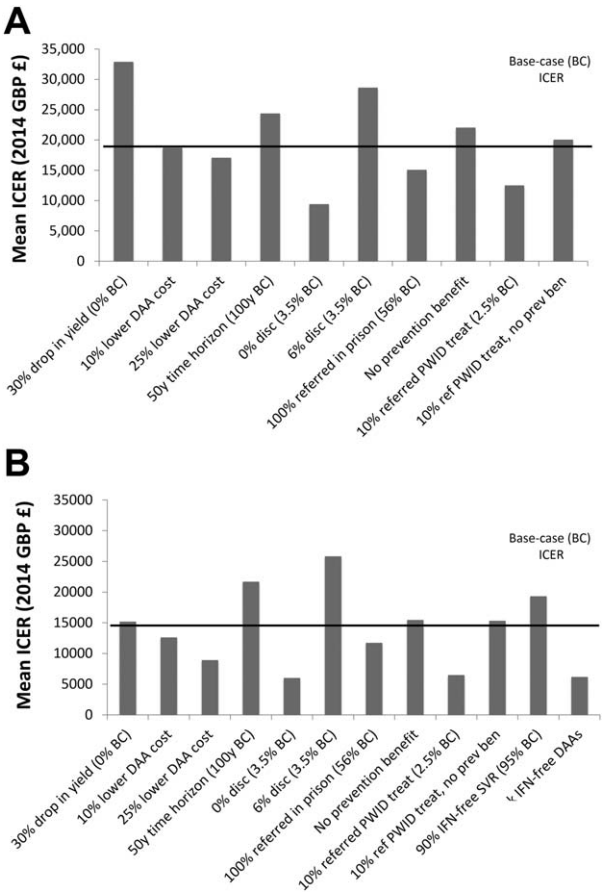

FIG. 3. One-way sensitivity analyses on mean ICERs. Black horizontal line denotes the base case ICER. (A) Doubled testing with status quo treatments compared to status quo testing/treatment. (B) Double testing with 8-week to 12-week IFN-free DAAs compared to doubled testing with status quo treatments. Abbreviations: BC, base case; GBP, British pounds; prev ben, prevention benefit.

EPIDEMIC IMPACT

Our model shows that baseline/existing levels of HCV treatment for PWID in prison and the community are unlikely to result in observable changes in HCV chronic prevalence or incidence among PWID in prison in the next 50 years (<9% relative reduction, Supporting Information). Negligible additional impact on HCV chronic prevalence or incidence among PWID in prison (<1% relative difference from baseline) is seen with doubled HCV testing in prison due to the low baseline treatment rates for PWID in prison. Similarly, doubled prison testing would only further reduce the cumulative incidence of hepatocellular carcinoma, liver transplant, or HCV-related deaths among the entire population by an additional 1% over the next 50 years. Even with doubled HCV testing in prison and a switch to 8-week to 12-week DAAs in prison, combined with a scale-up of HCV treatment such that 25% of PWID are treated after referral in prison, the modest reductions (12% relative reduction) in chronic prevalence or incidence occur among PWID in prison in 50 years. This is due to the low effective treatment rates for PWID given the gaps in the cascade of care from testing to SVR.

Discussion

We found that increased HCV testing in prison in England—such as that based on an opt-out intervention, which doubled HCV testing in pilot prisons—is borderline cost-effective with current treatments compared to status quo voluntary risk-based testing and is likely to be cost-effective if shorter-course IFN-free DAA therapy is used in prison under a £20,000 WTP

threshold. Increased HCV testing could be highly cost-effective (mean ICER <£13,000/QALY gained) if the cascade of care is improved through increasing PWID treatment rates. For example, if >10% PWID are treated after referral in prison (four times higher than the 2.5% base case), then doubled testing in prison is estimated to have a mean ICER of <£13,000/QALY gained. Cost-effectiveness is influenced by population prevention benefits—averting secondary infections in the community—and DAA costs. Without prevention benefits, HCV testing is above the £20,000 WTP, whereas increasing prevention benefit (through increasing PWID treatment rates) and decreasing costs could achieve cost-effectiveness below £13,000 WTP. However, even with 8-week treatments, SVR may be compromised without ensuring continuity of care or targeting treatment to people with slightly longer than average sentences.

STRENGTHS AND LIMITATIONS

A key strength of our model is the dynamic transmission component, such that cost-effectiveness includes both individual-level benefits (on prevention of disease progression) and population-level benefits (on prevention of HCV transmission among PWID). However, there are a number of limitations due to a lack of data on key parameters.

First, one of the main drivers of cost-effectiveness is the fall-off from different stages in the cascade of care, such as referral and treatment rates. Unfortunately, limited data are available on these rates across the prison system and no data stratified by injecting risk status.[25] Our referral rate in prison is based on empirical evidence from three prisons but may not be representative nationally, though we do include wide uncertainty. Furthermore, the model allocates treatment randomly, which can compromise effective SVR. Although in some prisons patients are selected for treatment in part based on duration of stay, it is unclear how widespread this practice is and what implications this has on PWID treatment rates (which, if reduced, will adversely affect cost-effectiveness but if treatment completion is increased, then cost-effectiveness will improve substantially). Additionally, there is a lack of data on disease stage among prisoners, which may impact treatment eligibility and treatment rates with IFN-free DAAs. Due to cost considerations, US and European guidelines recommend prioritizing HCV treatment for those with advanced liver disease (F3/F4), and recent European guidelines also recommend treating people at risk of transmission such as PWID[26] irrespective of disease stage. However, it seems more likely that the United Kingdom and other countries in Europe will prioritize treatment based on disease stage.[27] HCV patients within prisons (especially PWID) are generally younger with less advanced disease and thus could be less likely to receive IFN-free DAA therapies. Clinicians treating such cohorts within and outside prisons may be inclined to defer therapy in the hope that they may become eligible for safer, better-tolerated regimes as the guidelines are revised with a decline in costs over time. Also, cirrhosis assessment requires additional investigations, which may prolong assessment time and reduce time for treatment. Indeed, despite relatively short reported times to referral from the phase 1 "pathfinder prisons" (<4 weeks), the standard against which prison performance is measured is 18 weeks, so if delays to referral and during assessment occur, this could further limit the number of PWID who can be successfully treated in prison. Therefore, shorter IFN-free DAA therapy may not necessarily translate into greater access to treatment within prison, particularly among PWID, in the absence of continuity of care arrangements with the community.

Second, we used preliminary data from the opt-out pilot program to inform our assumptions surrounding impact on testing rates and, therefore, model a doubling of HCV testing rates as achieved in these pilot prisons, but the impact when fully implemented is unclear. However, other interventions to increase HCV testing in UK prisons have been unsuccessful.[28]

Third, there is uncertainty regarding SVR rates with IFN-free DAA therapies among PWID and prisoners. Systematic reviews have shown comparable SVR with IFN-based therapies among PWID and noninjecting populations, and preliminary trials with IFN-free DAAs among PWID on opiate substitution therapy indicate no difference in SVR compared to noninjectors. Nevertheless, we show that IFN-free DAAs in prison are likely cost-effective even with lower SVR rates (90%) and that an important driver will be "effective SVR" related to treatment completion.

Fourth, due to a lack of data, we assumed no continuity of treatment between prison and community such that those who are released while on treatment or in referral for treatment are assumed lost to follow-up and require retesting and reengagement. Providing effective continuity of care should increase the proportion successfully treated after diagnosis (whether in prison or the community) and could likely increase

cost-effectiveness.[3] Currently, some patients diagnosed in prison choose to defer treatment until they return to the community for such reasons such as fear of stigma within prison and the desire for a family/peer support network during treatment. Therefore, cost-effectiveness and public health impact will be affected by how well continuity of care is ensured across custodial and community settings, and efforts should be made to strengthen these transitions.

Fifth, due to a lack of data on HCV prevalence among PWID in prison, we modeled a 35% chronic prevalence among all PWID,[11] which corresponds to a similar prevalence among incarcerated PWID based on the age distribution of incarceration rates among PWID. However, if HCV prevalence/incidence among PWID in prison is lower than that in the community, HCV treatment in prison may have more prevention benefit and may be more cost-effective. Additionally, we assumed proportional mixing by age among PWID in prison (and the community) due to a lack of data to suggest otherwise. However, if PWID mix partially assortatively by age in prison, such that young PWID mix more with young PWID, this could lead to a lower HCV chronic prevalence among PWID in prison than we modeled and, consequently, greater treatment as prevention benefits.

Sixth, we assumed no improvement in fibrosis score upon successful treatment with DAAs, despite evidence that fibrosis regression may occur in a portion of patients after DAA therapy, although the particular patients who benefit, the degree of benefit, and the timing of improvement are uncertain.[29,30] However, our analysis found HCV testing and DAA therapy highly likely to be cost-effective, and including improvement in fibrosis would increase cost-effectiveness further.

Seventh, we assumed no behavior change after HCV testing or treatment due to a lack of strong evidence in this area. Two small studies have found decreases in injecting risk behavior with a positive HCV diagnosis[31,32]; however, a recent large prospective pooled analysis among 829 PWID in Canada, the United States, The Netherlands, and Australia found no evidence of injecting risk behavior change for PWID after a positive or negative HCV diagnosis.[33] If HCV testing reduces risk among those with or without HCV, this would further improve any case-finding intervention. Additionally, it is possible individuals will reduce their risk following successful treatment, which would also increase the cost-effectiveness of HCV treatment.

COMPARISON WITH OTHER STUDIES

Two previous IFN-based studies using static models (ignoring prevention benefit in the community) suggested that HCV testing in UK prisons was unlikely to be cost-effective.[34,35] Our previous analysis found that increased HCV testing in English prisons was unlikely to be cost-effective (ICER ~£60,000/QALY gained) with IFN/RBV treatment due to a combination of short incarceration durations (4/8 months for PWID/non-PWID, respectively), long treatment durations (24-48 weeks), and a lack of continuity of care between prison and the community.[3] In contrast, our current analysis suggests that HCV case-finding in English prisons is borderline cost-effective with currently available therapies and more likely to be cost-effective with highly effective short-course IFN-free DAA therapies. Our study supports a recent dynamic modeling study in the United States which found that opt-out testing in prison with DAAs is likely cost-effective, but their study assumed much higher rates of testing uptake (90% compared to 12% in our study based on pilot data) as well as behavior change after diagnosis and treatment (which we did not assume).[36]

IMPLICATIONS

Prisons can be an important contributor to bloodborne virus risk for PWID[37] but can also play a role in public health prevention. Prisoners should receive the same standard of care as people in the community; however, interventions do need to be cost-effective. HCV case-finding among PWID in the community is cost-effective, but because continuity of care could not be guaranteed between prison and the community, it was unlikely to be cost-effective in prison. We show that the arrival of shorter (and more effective) HCV treatment regimens, which means that more prisoners can complete treatment prior to release, alters the cost-effectiveness decision. Treatment uptake in prison, as well as IFN-free DAA therapy cost, now are the main drivers of cost-effectiveness of HCV case-finding. In addition, cost-effectiveness is predicated on the "prevention benefit" of reducing HCV transmission in the community through successfully treating PWID, which requires empirical demonstration. Further, enhanced data collection of the cascade of care in prison, as will be achieved through the new Health and Justice Information Service, will allow for better

monitoring and evaluation of prison HCV testing and treatment programs in the future.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28497/suppinfo.